

REMARKS**I. Status of the Claims**

Claims 1, 4, 10, 12 and 21-30 are pending, with claims 1, 4, 10, 12 under consideration, and claims 21-30 withdrawn from consideration as being drawn to non-elected groups. Claim 1 is amended herewith. After entry of this Amendment, claims 1, 4, 10, 12 remain pending and under consideration. Furthermore, because the Examiner required restriction between the product and process claims, upon finding the product claims allowable, Applicants respectfully requests rejoinder of the withdrawn process claims.

The amendments of the specification and the various rejections raised in the Office Action are discussed in more detail, below.

II. Amendments to the Specification

Applicants thank the Examiner for noting the discrepancy between the description of the PAP/GM-CSF fusion protein in the specification at page 17, lines 22-30 and SEQ ID NO:5 presented in the sequence listing. Applicants have amended the specification, and further note that, as recognized by the Examiner on page 8 of the Office Action dated 20 April 2007, the construction of this fusion protein is described in Example 1. Moreover, this fusion protein is stated to be previously described in U.S. Patent Nos. 5,976,546, 6,080,409, and 6,210,662, which were incorporated by reference into the present application at the time of filing.

No new matter is added by way of these amendments to the specification.

III. Amendments to the Claims

Claim 1 has been amended to make clear that the APCs are obtained from a single patient diagnosed with prostate cancer having a moderate- to well-differentiated cancer grade and a Gleason score of 7 or less, as well as to add punctuation marks to the SEQ. ID. NOs.

IV. Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 4, 10 and 12 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most connected to make and use the presently claimed immunotherapeutic composition commensurate in scope with the claims.

This rejection is respectfully traversed in view of the following.

A. Enablement

1. Legal Standard

When rejecting a claim under the enablement clause of 35 U.S.C. § 112, first paragraph, the Patent Office bears the initial burden of setting forth a reasonable explanation as to why it believes the scope of protection provided by that claim is not adequately enabled by the description of the claimed invention provided in the specification of the application. See M.P.E.P. § 2164.04.

The rejection appears to be based on the Examiner's notion that the inclusion of the phrase "consisting essentially of" in the claim allows the claim scope to encompass additional elements which would materially affect the composition. The Examiner alleges that "the claimed immunostimulatory composition is not enabled because the claims encompass other elements with the fusion protein that may potentially materially effect the basic and novel characteristics of the composition" (Office Action at page 5). Applicants disagree.

In fact, the courts have interpreted the claim language "consisting essentially of" to signal a partially open claim which is open to unlisted elements that **do not materially affect** the basic and novel properties of the invention. The "*partially open*" quality of this claim language is meant to specifically exclude elements that do materially affect the basic characteristics of the claimed subject matter. (See *PPG Industries v. Guardian Industries, Corp.*, 156 F.3d 1351, 48 USPQ2d 1351 (Fed. Cir. 1998); and *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984)).

Accordingly, Applicants submit that the ordinarily skilled artisan would understand that the subject matter as presently claimed does not include additional factors that would materially change the basic characteristics of the presently claimed subject matter. Furthermore, the specification clearly enables any person skilled in the art to which it pertains to make and use the presently claimed subject matter.

In light of the teaching in the specification and Applicants' amendments, Applicants submit that the present claims satisfy the requirements of 35 U.S.C. §112, first paragraph and respectfully request that this rejection be withdrawn.

V. Rejection under 35 U.S.C. § 102

Claims 1, 4, 10 and 12 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Small *et al.* (of record), as evidenced by Ahmed *et al.* (of record).

Claims 1, 4, 10 and 12 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Burch *et al.* (of record), as evidenced by Ahmed *et al.* (of record).

These rejections are respectfully traversed.

A. The Present Claims

The present claims relate to an immunotherapeutic composition, comprising activated, isolated antigen presenting cells (APCs), wherein said APCs are obtained from a single patient diagnosed with prostate cancer having a moderate- to well-differentiated cancer grade and a Gleason score of 7 or less and wherein said APCs are stimulated by exposure *ex vivo* to a fusion protein consisting essentially of human prostatic acid phosphatase (huPAP) of SEQ. ID. NO:1 and human granulocyte-macrophage colony stimulating factor (huGM-CSF) of SEQ. ID. NO: 3.

B. The Cited Art

SMALL ET AL. describe clinical trials with dendritic cells stimulated using a recombinant fusion protein of PAP linked to GM-CSF, wherein the study patients had hormone-refractory prostate cancer and an expected survival of at least 3 months, suggesting that many of the cancers had advanced and were not treatable by androgen deprivation. Small is silent with regard to Gleason score of the prostate cancer in each patient in the pool. However, the androgen-refractory nature of the prostate cancer in all the patients, and the metastatic state of some of the patients indicates that many of the patients in the Small reference would be expected to have a Gleason score greater than 7.

AHMED ET AL. describe the examination of a collection of prostate biopsies to determine the incidence of prostate adenocarcinoma and the correlation of the presence of tumor with the Gleason scoring system. The Ahmed reference states that the majority of tumors biopsied were moderate to poorly differentiated. The Ahmed reference does not supply the Gleason score of any patient in the androgen-refractory patient pool of Small.

BURCH ET AL. describe a phase I clinical trial in which humoral immunity was induced in patients suffering from progressive hormone-refractory metastatic prostate carcinoma using autologous dendritic cells (APC8015) pre-exposed *ex vivo* to PA2024, a fusion protein consisting of human GM-CSF and human PAP. Burch *et al.* is silent with respect to the Gleason score of each of the thirteen patients in the study, however the fact that all of these patients had advanced metastatic cancers refractory to hormone treatment suggests that these patients would be expected to have a Gleason score greater than 7.

C. Analysis

The Examiner alleges that “none of the instant claims are specifically limited to the composition comprising APC’s from a prostate cancer patient with *only* moderate to well differentiated cancer grade and *only* a Gleason score of 7 or less. The claims necessarily encompass APC’s from patients of mixed grade and mixed Gleason score” (Office action at pages 6-7; emphasis in original). As presently amended, the claims clearly require that the APCs are taken from a single patient, and that the prostate cancer has a moderate- to well-differentiated cancer grade with a Gleason score of 7 or less. The present claims do not encompass patients with cancers having a “mixed grade and mixed Gleason score.”

Firstly, the Examiner’s broad conclusory statement that “the claims encompass APC’s from patients of mixed grade and mixed Gleason score” is unfounded. The Examiner has presented no evidence of a patient with a “mixed grade and mixed Gleason score.” It is known in the art that a final Gleason score is the sum of two scores, each ranging from one to five: the “primary grade” represents the majority of the prostate tumor (observed in greater than 50% of the total pattern), and the “secondary grade” represents the minority of the tumor (between 5 and 50% of the pattern of the total prostate cancer). These scores are then added to obtain a final Gleason score. Unless the Examiner means to say that two different diagnosticians may assess a prostate tumor and each arrive at a different Gleason score for the same patient, Applicants respectfully submit that it is unclear how a single patient can have a “mixed” Gleason score. Toward this point, an expert declaration accompanies this Amendment.

Moreover, the standard for lack of novelty, that is, for anticipation, is one of strict identity. The Small reference describes a clinical trial conducted with advanced stage prostate cancer patients, implying relatively high Gleason scores, likely to exceed the presently claimed Gleason score of 7 or less. Similarly, the Burch reference describes a study of prostate cancer patients all of whom had advanced metastatic cancers refractory to hormone treatment, suggesting that the cancers were poorly differentiated and would be expected to have a Gleason score greater than 7. Thus, the patient pools of the Small and Burch references represent a different cross-section of patients than that presently claimed, and thus, do not provide evidence of strict identity, and therefore cannot anticipate the presently claimed subject matter.

Neither the Small reference nor the Burch reference identifies the Gleason score of a single patient in their studies; however, from the advanced, hormone-refractive and metastatic nature of the cancers in these studies, it is likely that the cross-section of patients studied would have poorly differentiated cancers having Gleason scores higher than 7. The Examiner relies on the Ahmed

reference solely for its association, in the pool of biopsy specimens collected, of moderately differentiated prostate cancers with a Gleason's score of 5, 6 or 7. However, Ahmed specifically states that "(g)rating was not possible in most core biopsies" and that the "(m)ajority of tumours were moderate to poorly differentiated" (See abstract). Thus, the collection of biopsies of Ahmed showing cancers that were moderate- to poorly-differentiated is not strictly identical to the presently claimed patient diagnosed with prostate cancer having a moderate- to well-differentiated cancer grade and a Gleason score of 7 or less. Not only do the Small, Burch and Ahmed references describe a different patient population than that presently claimed, but the Ahmed reference is irrelevant to, and in no way strengthens the Examiner's case for anticipation based on the Small or Burch references, as it does not provide any evidence of anticipation of the presently claimed "patient diagnosed with prostate cancer having a moderate- to well-differentiated cancer grade and a Gleason score of 7 or less."

In the present application, Applicants have newly discovered that a specific subset of patients having prostate cancer are amenable to treatment with the presently claimed composition, whereas others are refractory. As cancer advances and Gleason scores increase, cancerous cells become more poorly differentiated and Applicants have shown that patients with higher Gleason scores are more refractory to treatment with the composition of the present claims. (See Example 4 of the specification as filed, which illustrates that a specific subset of patients having a Gleason score of ≤ 7 treated with the presently claimed composition exhibits a statistically significant enhancement in median T-cell mediated immune response as compared to a patient population having a Gleason score of ≥ 8 treated with the composition). The Small and Burch studies describe a different cross-section of patients, a subset which may overlap with, but is distinct from the scope of the present claims. The fact that the patient population may overlap with the presently claimed patient population by encompassing patients with moderately-differentiated cancer is insufficient to be anticipatory, as the Small and Burch references fail to disclose with sufficient specificity patients having any particular Gleason scores, much less those having a Gleason score of 7 or less. In this situation, the M.P.E.P clearly states:

When the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. See, *e.g.*, *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991,

999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Id.* at 1000, 78 USPQ2d at 1424. Any evidence of unexpected results within the narrow range may also render the claims unobvious. The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching.

(See MPEP § 2131.02). The Small and Burch references clearly lack the "sufficient specificity" to describe the presently claimed patient population having moderate- to well-differentiated prostate cancer and a Gleason score of 7 or less.

As presently claimed, the immunotherapeutic composition is enabled for the full scope of the claims. Accordingly, Applicants submit that standard of strict identity to maintain a rejection under 35 U.S.C. § 102 has not been met and withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

VI. Rejection under 35 U.S.C. §103

Claims 1, 4, 10 and 12 stand rejected under 35 U.S.C. §103 as allegedly obvious over Laus *et al.* (of record) in view of Small *et al.* (of record) as evidenced by Ahmed *et al.* (of record). According to the Patent Office, "it is more than apparent that one skilled in the art based on the combination of references could have drawn a convincing line of reasoning based on the established scientific principles of the references that some advantage or expected beneficial result would have been produced by their combination." (Office Action at page 9). Applicants disagree for at least the reasons explained below.

A. The Present Claims

The present claims relate to an immunotherapeutic composition comprising activated, isolated antigen presenting cells (APCs), wherein said APCs are obtained from a single patient diagnosed with prostate cancer having a moderate- to well-differentiated cancer grade and a Gleason score of 7 or less and wherein said APCs are stimulated by exposure *ex vivo* to a fusion protein consisting essentially of human prostatic acid phosphatase (huPAP) of SEQ. ID. NO:1 and human granulocyte-macrophage colony stimulating factor (huGM-CSF) of SEQ. ID. NO: 3.

B. The Cited Art

LAUS ET AL. describes APC compositions stimulated with a protein complex of a dendritic cell binding protein and a polypeptide antigen.

The Small and Ahmed references are discussed above.

C. Analysis

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Moreover, whether or not a skilled artisan "could have drawn a convincing line of reasoning based on the established scientific principles of the references that some advantage or expected beneficial result would have been produced by their combination" (Office Action at page 9, emphasis added) is not the proper legal standard for a finding of obviousness. As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, S. Ct. 1727 (2007); 82 USPQ2d 1385, 1397 (2007), the factors stated in *Graham v. John Deere*, 383, U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry. Thus, a determination of obviousness requires an objective analysis involving four factual inquiries: (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claims at issue, (3) resolving the level of ordinary skill in the art; and (4) evaluating evidence of secondary conditions.

The standard is not whether or not the skilled artisan could combine the references and find some advantage or beneficial result produced by the combination. Rather a finding of obviousness depends on recognition by the skilled artisan that the particular combination of references would necessarily achieve the presently claimed subject matter. The Examiner has provided no reasoning or evidence demonstrating the particular "convincing line of reasoning based on the established scientific principles of the references" that would lead the skilled artisan to arrive at the presently claimed subject matter.

Like the other cited references, the Laus reference fails to teach or suggest selection, from all prostate cancer patients, the specific subset of prostate cancer patients with moderate-to well-differentiated prostate cancer having a Gleason score of 7 or less from which APCs are obtained and stimulated for inclusion in the immunotherapeutic composition as presently claimed. Furthermore, the secondary references, Small and Ahmed, fail to cure the deficiency of the Laus reference, as noted in the 102(b) discussion above.

The standard for obviousness as set forth in the KSR decision presumes a finite and, in the context of the art, small or easily traversed number of options. (See *KSR International Co. v. Teleflex Inc.*, S. Ct. 1727 (2007); and *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.* (Fed. Cir. 2008)). In contrast, in the present case, the skilled artisan at the time of this invention had no reason to select, from the myriad means of characterizing prostate cancer grades, the specific patient population of the current claims. The art relied upon by the

Examiner fails to teach or even suggest assessment of Gleason scores nor the selection of a subset of patients having moderate- to well-differentiated prostate cancers having a Gleason score of 7 or less.

Applicants found unexpected and surprising properties of the presently claimed composition: it was unknown that prostate cancer patients with a Gleason score of 7 or less would exhibit a significantly enhanced response as compared to patients with a Gleason score of 8 or greater to the presently claimed composition.

In view of the fact that the cited references fail to teach all the elements of the present claims, as well as the lack of reasonable expectation that a skilled artisan would have the prescience to select the particular patient population of the presently claimed subject matter to achieve the composition as presently claimed, Applicants submit that the claims are novel and non-obvious, patentably defining over the cited art, and respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

In light of the foregoing remarks, claims 1, 4, 10, 12 and 21-30 are believed to satisfy all of the criteria for patentability and are in condition for Allowance. An early indication of the same is therefore kindly requested.

No fees, other than the fee for a three-month extension of time, are believed to be due in connection with this Amendment. However, the Commissioner is authorized to charge any additional fees that may be required, or credit any overpayment, to King & Spalding LLP Deposit Account No. 50-4616.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 590-1932.

Respectfully submitted,
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